

IN THE CLAIMS

1. (Currently amended) A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively degrading either hybridized, partially hybridized or unhybridized ~~nucleic acid~~ oligonucleotide probe, the degrading resulting in degraded oligonucleotide probe; and electrochemically determining information relating to the electrochemically active marker, wherein the information relating to the electrochemically active marker correlates with the presence of the nucleic acid and wherein the information relating to the electrochemically active marker correlates with the size and characteristics of the degraded or non-degraded oligonucleotide probe, the method resulting in probing for the nucleic acid.
2. (Original) A method as claimed in claim 1 wherein the information relating to the marker is used to derive information concerning the presence or absence of at least one nucleic acid species.
3. (Currently amended) A method as claimed in claim 1 wherein the electrochemical technique is used to quantify relative proportions of degraded and non-degraded oligonucleotide probe.
4. (Currently amended) A method as claimed in claim 1 wherein ~~nucleic acid~~ oligonucleotide probe that has failed to successfully hybridize is digested by an enzyme that has been chosen to selectively digest single stranded unhybridized nucleic acid.
5. (Original) A method as claimed in claim 4 wherein the enzyme is an endonuclease.
6. (Previously amended) A method as claimed in claim 4 wherein the enzyme is a ribonuclease.
7. (Previously amended) A method as claimed in claim 4 herein the enzyme is a deoxyribonuclease.
8. (Previously amended) A method as claimed in claim 4 wherein the enzyme is S1 deoxyribonuclease.

9. (Previously amended) A method as claimed in claim 4 wherein the enzyme is an exonuclease.
10. (Canceled)
11. (Currently amended) A method as claimed in claim 1 wherein ~~nucleic acid~~ oligonucleotide probe that has successfully hybridized is digested by an enzyme that has been chosen to selectively digest at least one strand of double stranded hybridized nucleic acid.
12. (Original) A method as claimed in claim 11 wherein the enzyme is a 5' nuclease.
13. (Original) A method as claimed in claim 12 wherein the 5' nuclease is also a DNA polymerase.
14. (Original) A method as claimed in claim 13 wherein the 5' nuclease/DNA polymerase is a thermostable enzyme.
15. (Original) A method as claimed in claim 14 wherein the thermostable enzyme is Taq polymerase.
16. (Previously amended) A method as claimed in claim 14 wherein the nucleic acid solution also comprises a pair of primers suitable for extension by the DNA polymerase.
17. (Original) A method as claimed in claim 16 wherein reaction conditions and temperature cycling are suitable for a polymerase chain reaction (PCR) to take place concomitant to the 5' nuclease digestion of probe.
18. (Previously amended) A method as claimed in claim 1, in which a first oligonucleotide probe labeled with an electrochemically active marker is prevented from complete hybridization by competition from a second oligonucleotide, and the resultant partially hybridized oligonucleotide labeled with an electrochemically active marker is cleaved by an enzyme that specifically recognizes the configuration of the two oligonucleotides hybridized onto the target nucleic acid, said cleavage effectively shortening the oligonucleotide portion to which the electrochemically active marker is attached.

19. (Previously amended) A method as claimed in claim 1, in which a first oligonucleotide probe is prevented from complete hybridization by competition from a second oligonucleotide, and the resultant partially hybridized first oligonucleotide probe is cleaved by an enzyme that specifically recognizes the configuration of the two oligonucleotides hybridized onto the target nucleic acid, the cleavage product being recognized by a recognition cassette which comprises at least one oligonucleotide and is able to hybridize to the first cleavage product to produce an oligonucleotide configuration recognizable by an enzyme that cleaves a region of the recognition cassette that is labeled with an electrochemically active marker.

20. (Previously amended) A method as claimed in claim 1 wherein the electrochemically determined information is used for the detection of nucleic acid polymorphisms.

21. (Previously amended) A method as claimed in claim 1 wherein the electrochemically determined information is used for detection of allelic polymorphisms.

22. (Previously amended) A method as claimed in claim 1 wherein the electrochemically determined information is used for the detection of single nucleotide polymorphisms.

23. (Previously amended) A method as claimed in claim 1 wherein the electrochemically determined information is used for the quantification of nucleic acid species.

24. (Previously amended) A method as claimed claim 1 wherein the electrochemically determined information is used for the quantification of gene expression.

25. (Previously amended) A method as claimed in claim 16 wherein primer design and/or probe design and/or thermal cycling and detection of electrochemically active marker is carried out automatically or with the assistance of a software-directed microprocessor.

26. (Canceled)

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42. (Canceled)

43. (Previously amended) A method as claimed in claim 1 wherein the electrochemically determined information is used for the detection of a genetic disease or a genetic disease carrier status or a genetic predisposition to disease.

44. (Previously amended) A method as claimed in claim 1 wherein the electrochemically determined information is used to detect or identify a pathogen in a sample.

45. (Previously amended) A method as claimed in claim 1 wherein the electrochemically determined information is used to predict a response of an organism to a therapeutic or toxic agent.

46. (Canceled)

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90. (Canceled)

91. (Previously amended) A method as claimed in claim 1 in which two or more oligonucleotide probes are used, each probe being labeled with a different electrochemically active marker.

92. (Original) A method as claimed in claim 91 in which the two or more electrochemically active markers have peaks in their voltammogram traces that are resolvable from each other.

93. (Previously presented) A method as claimed in claim 12, wherein the enzyme is T7 exonuclease.

94. (Previously presented) A method as claimed in claim 24 wherein the unhybridized nucleic acid is degraded by an enzyme.

95. (Previously presented) A method as claimed in claim 94 wherein the enzyme is an endonuclease.

96. (Previously presented) A method as claimed in claim 94 wherein the enzyme is a ribonuclease.

97. (Previously presented) A method as claimed in claim 94 wherein the enzyme is a deoxyribonuclease.

98. (Previously presented) A method as claimed in claim 94 wherein the enzyme is S1 deoxyribonuclease.

99. (Previously presented) A method as claimed in claim 1 wherein the electrochemical step is voltammetry.

100. (Previously presented) A method as claimed in claim 1 wherein the electrochemical step is an amperometric technique.

101. (Previously presented) A method as claimed in claim 1 wherein the electrochemical step is differential pulse voltammetry.

102. (Previously presented) A method as claimed in claim 1 wherein the electrochemical technique utilizes one or more electrodes that have been functionally surrounded by a selectively permeable membrane.

103. (Previously presented) A method as claimed in claim 102 wherein the membrane is selectively permeable on the basis of molecular size.

104. (Previously presented) A method as claimed in claim 102 wherein the membrane is selectively permeable on the basis of charge.

105. (Previously presented) A method as claimed in claim 102 wherein the membrane is selectively permeable on the basis of hydrophobicity or hydrophilicity.

106. (Canceled)

107. (Canceled)

108. (Canceled)

109. (New) A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the probe is able to at least partially hybridize with any

complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively digesting hybridized oligonucleotide probe using a duplex specific exonuclease; and electrochemically determining information relating to the electrochemically active marker, wherein the information relating to the electrochemically active marker correlates with the presence of the nucleic acid and wherein the information relating to the electrochemically active marker correlates with the extent of digestion of the oligonucleotide probe, the method resulting in probing for the nucleic acid.

110. (New) A method as claimed in claim 109 wherein the exonuclease is selected from the group consisting of a duplex specific exonuclease, a 5'-3' exonuclease, a 3'-5' exonuclease, and T7 nuclease.

111. (New) A method as claimed in claim 109 wherein the exonuclease is a 5'-3' exonuclease.

112. (New) A method as claimed in claim 109 wherein the information relating to the marker is used to derive information concerning the presence or absence of at least one nucleic acid species.

113. (New) A method as claimed in claim 109 wherein the electrochemical technique is used to quantify relative proportions of degraded and non-degraded oligonucleotide probe, if present.

114. (New) A method as claimed in claim 111 wherein the 5'-3' nuclease is also a DNA polymerase.

115. (New) A method as claimed in claim 114 wherein the nucleic acid solution also comprises a pair of primers suitable for extension by the DNA polymerase.

116. (New) A method as claimed in claim 115 wherein reaction conditions and temperature cycling are suitable for a polymerase chain reaction (PCR) to take place concomitant to the 5' nuclease digestion of probe.

117. (New) A method as claimed in claim 109, in which a first oligonucleotide probe labeled with an electrochemically active marker is prevented from complete hybridization by competition from a second oligonucleotide, and the resultant partially hybridized oligonucleotide labeled with an electrochemically active marker is cleaved by an enzyme that specifically recognizes the configuration of the two oligonucleotides hybridized onto the target nucleic acid, said cleavage effectively shortening the oligonucleotide portion to which the electrochemically active marker is attached.

118. (New) A method as claimed in claim 109, in which a first oligonucleotide probe is prevented from complete hybridization by competition from a second oligonucleotide, and the resultant partially hybridized first oligonucleotide probe is cleaved by an enzyme that specifically recognizes the configuration of the two oligonucleotides hybridized onto the target nucleic acid, the cleavage product being recognized by a recognition cassette which comprises at least one oligonucleotide and is able to hybridize to the first cleavage product to produce an oligonucleotide configuration recognizable by an enzyme that cleaves a region of the recognition cassette that is labeled with an electrochemically active marker.

119. (New) A method as claimed in claim 109 wherein the electrochemically determined information is used for the detection of nucleic acid polymorphisms.

120. (New) A method as claimed in claim 109 wherein the electrochemically determined information is used for detection of allelic polymorphisms.

121. (New) A method as claimed in claim 109 wherein the electrochemically determined information is used for the detection of single nucleotide polymorphisms.

122. (New) A method as claimed in claim 109 wherein the electrochemically determined information is used for the quantification of nucleic acid species.

123. (New) A method as claimed claim 109 wherein the electrochemically determined information is used for the quantification of gene expression.

124. (New) A method as claimed in claim 115 wherein primer design and/or probe design and/or thermal cycling and detection of electrochemically active marker is carried out automatically or with the assistance of a software-directed microprocessor.

125. (New) A method as claimed in claim 109 in which two or more oligonucleotide probes are used, each probe being labeled with a different electrochemically active marker.

126. (New) A method as claimed in claim 125 in which the two or more electrochemically active markers have peaks in their voltammogram traces that are resolvable from each other.

127. (New) A method as claimed in claim 109 wherein the electrochemical step is voltammetry.

128. (New) A method as claimed in claim 109 wherein the electrochemical step is an amperometric technique.

129. (New) A method as claimed in claim 109 wherein the electrochemical step is differential pulse voltammetry.

130. (New) A method as claimed in claim 109 wherein the electrochemical technique utilizes one or more electrodes that have been functionally surrounded by a selectively permeable membrane.

131. (New) A method as claimed in claim 130 wherein the membrane is selectively permeable on the basis of molecular size.

132. (New) A method as claimed in claim 130 wherein the membrane is selectively permeable on the basis of charge.

133. (New) A method as claimed in claim 130 wherein the membrane is selectively permeable on the basis of hydrophobicity or hydrophilicity.